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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,586	12/20/2001	Vanessa Chisholm	P1746R1	1705

9157 7590 05/11/2010

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EXAMINER	
SGAGIAS, MAGDALINE K	
ART UNIT	PAPER NUMBER
1632	
MAIL DATE	DELIVERY MODE
05/11/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/019,586	CHISHOLM ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *151 and 153-160* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *151 and 153-160* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 01/28/2010 have been fully considered. The amendment has been entered. Claims 1-150, 152, 161-164 are canceled. Claims 151, 153-160 are pending and under consideration.

Claim Rejections - 35 USC § 103/Necessitated by Amendment

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims **151, 153-160** under 35 U.S.C. 103(a) as being unpatentable over **Crowley** (US 5,561,053 (IDS) in view of **Liu et al** (WO/1995/024485, published 09/14/1995, IDS); **Mosser et al,** Biotechnique 22:150-154, 1997 (IDS); **Bennett et al** (BioTechniques, 24(3): 478-482, 1998 (IDS); **Tan et al,** (US 6,235,967; see whole document; hereinafter the '967 patent (IDS); **Chishima et al,** (Cancer Res. 1997; 57:2042-47 (IDS) is withdrawn in view of the amendment.

Claims **151, 153-160** are rejected under 35 U.S.C. 103(a) as being unpatentable over Crowley (US 5,561,053 (IDS) in view of Liu et al (WO/1995/024485, published 09/14/1995, IDS); Mosser et al, Biotechnique 22:150-154, 1997 (IDS); Bennett et al (BioTechniques, 24(3): 478-482, 1998 (IDS); Tan et al, (US 6,235,967; see whole document; hereinafter the '967 patent (IDS); Chishima et al, (Cancer Res. 1997; 57:2042-47 (IDS) **and further in view of Zolotukhin et al,** (US 5874304 A).

Crowley teaches a method of obtaining a cell expressing a desired product, the method comprising: **a)** introducing into mammalian cells a vector comprising: **(i)** a single transcription unit comprising a promoter, an intron positioned 3' to the promoter and a polynucleotide encoding the desired product positioned to the intron; **(ii)** a polynucleotide encoding an amplifiable selectable marker dihydrofolate reductase (DHFR), wherein the intron is defined by a 5' splice donor site and a 3' splice acceptor site such that the efficiency of splicing messenger RNA having said splice donor sequence is between 80% and 99% as determined by quantitative PCR, and a 3' acceptor site; and wherein the polynucleotide encoding the desired product and the promoter are operably linked to the polynucleotide encoding the DHFR selectable marker; **b)** isolating the cells by culturing the cells under conditions that preferentially allow for the growth or survival of those cells that synthesize the DHFR selectable marker encoded by the selectable gene, wherein expression of the DHFR amplifiable selectable marker is indicative of the cell expressing the desired product; and **c)** recovering said desired product from said cells (columns 53-54, figures 1A-1D, and example 1-3). Crowley discloses the selectable gene is positioned within an intron defined by a splice donor site and a splice acceptor site and the selectable gene and product gene are under the transcriptional control of a single transcriptional regulatory region (abstract) **(claims 151, 159-160)**. Crowley teaches that the DHFR is the most widely used amplifiable gene which encodes a dihydrofolate reductase enzyme (column 2 bridge to column 3). The selection agent used in conjunction with a DHFR gene is methotrexate (Mtx). A host cell is cotransfected with a product gene encoding a desired protein and a DHFR gene, and transfectants are identified by first culturing the cells in culture medium that contains Mtx (column 2 bridge to column 3) **(claims 156, 158)**. Crowley discloses the transfected cells are cultured so as to express the gene encoding the product in a

selective medium comprising an amplifying agent for sufficient time to allow amplification to occur, whereupon either the desired product is recovered or cells having multiple copies of the product gene are identified (abstract). Crowley discloses protein expression is measured using ELISA and the product of interest preferably is recovered from the culture medium as a secreted polypeptide, (column 17, lines 41-46) and purify the product of interest from recombinant cell proteins or polypeptides to obtain the product of interest for example, by fractionation on immunoaffinity (column 17, lines 46-63). Crowley differs from the present invention for not teaching a second transcription unit comprising a second promoter and an intron positioned 3' of the second promoter; and a polynucleotide encoding a green fluorescent protein (GFP).

However, at the time of the instant invention was made **Liu et al** teach a polynucleotide construct that induces the co- expression of three gene products, wherein the construct has a first eukaryotic promoter operatively linked to a first cistron, and a second cistron operatively controlled by its own promoter, and a third cistron downstream of the second cistron, operatively controlled by a third promoter, further containing a transcriptional terminator following each of the first, second and third cistron (see claim 1 of '485). It is also disclosed that the coordinate expression results in improved expression of the exogenous gene products which maybe otherwise poorly expressed in a single cell (see page 1 of '485). Additionally, Liu et al teach that direction of transcription by various promoters and the genes they control are in opposite directions (see page 19, lines 30-35). Liu et al indicates that vector modification and development procedures may be accomplished according to methods known in the art (see page 14, last line to page 15, lines 1-14). Liu et al teach that the DNA construct may use any known eukaryotic promoter including immunoglobulin promoter and polyadenylation terminator. Liu et al also disclose SV40 promoter and SV40 polyA in the construct. In a preferred embodiment, Liu et al teach use of CMV promoter and BGH polyA (page 4, line 23, and page

14, lines 14-15). Liu teaches multiple constructs, for example encoding gp l60, gpl 20, gp41 , or any other HIV gene may be prepared, mixed and co-administered and protein expression is maintained following DNA injection and standard techniques of molecular biology for preparing and purifying DNA constructs enable the preparation for example of DNA immunogens of this invention (p 34-35). Although Liu et al teach a nucleic acid construct comprising (a) a nucleotide sequence that encodes a first polypeptide operably linked to first promoter and a first polyadenylation signal; (b) a second transcriptional unit comprising a nucleotide sequence that encodes a second polypeptide operably linked to a second promoter and a second polyadenylation signal; (c) a third transcriptional unit comprising a nucleotide sequence that encodes a third polypeptide operably linked to a third promoter and a third polyadenylation signal, but differed from the claimed invention by not explicitly teaching use of the polynucleotide encoding a green fluorescence protein GFP in a transcriptional unit.

However, prior to instant invention the GFP selectable marker in dicistronic expression cassette was known in the art in a transcriptional unit. For instance, **Mosser et al** teach the use of plasmid containing a dicisronic expression cassette encoding GFP and a target gene, in a method of screening and selection of cells expressing inducible genes (p 152-153). Mosser suggests the dicistronic GFP plasmid can be used for identifying clones that stably express a tTA-regulated gene product and also to identify those cells that express a protein of interest following a transient transfection (p 154, 1st column). Mosser does not disclose the GFP for FACS sorting.

However, prior to instant invention use of GFP for cell sorting was known to one of ordinary of skill in the art. For instance, **Bennett et al** (BioTechniques, 24(3): 478-482, 1998) teaches that it is routine in the art to fuse GFP selectable marker with the Zeocin-resistance marker for the identification and selection of transfected mammalian cells (abstract). Bennett

reaches the GFP selectable marker provides a way to determine transient transfection efficiencies in tissue culture cells using fluorescence activated cell sorting (FACS) analysis (abstract, and p 482, 1st column). Expression of the GFP-ZeoR was also used to identify and select stable mammalian cell lines expressing a heterologous gene (abstract). Selection was efficient and GFP fluorescence provides an excellent, noninvasive technique to monitor the success of Zeocin selection during the development of the stable cell lines (abstract). Bennett suggests that FACS could be used for sorting cell populations with high or low levels of heterologous gene expression and to identify cell lines that overexpress therapeutic protein for purification (p 482, 1st column). Bennett teaches because plasmids are integrated as a single cassette, it is reasonable to assume that insertion at a transcriptionally active site that results in high-level expression of the fluorescent selectable marker would also have high expression of the heterologous gene (p 482, 1st column). **Tan et al** teaches in the '967 patent teaches a polynucleotide where GFP is fused to a selected sequence (e.g. methioninase or T antigen) and operably linked to a promoter. (e.g. Abstract; Fig. Ia). Furthermore, GFP can be of a higher fluorescence mutated (i.e. S65T) variety. (e.g. col. 3, 1. 26). In addition, various cell types can be transfected with the polynucleotide, including methotrexate selected CHO cells. (e.g. col. 3, line 63, col. 6, 11.27-37). Furthermore, the '967 indicates using a DHFR-GFP dicistronic vector (e.g. col. 6, Example 1; showing GFP-S65T mobilization into pED-mtx resistant) and explicitly teaches that such vector systems can be used to express proteins in mammalian cells. (e.g. col. 9, 11.40-45). The '967 patent doesn't expressly provide a construct where a target gene is operably linked to either a gene encoding GFP or a gene encoding an amplifiable selectable marker, where the construct comprises both genes regardless. Furthermore, the '967 patent teaches that a dicistronic vector comprising both a fluorescence encoding gene (i.e. GFP) and an amplifiable selectable marker (i.e. DHFR) can be used. (e.g. col. 9, II. 40-45). In addition, the

'967 patent teaches that said polynucleotides can be used for production of a fusion protein (e.g. GFP-T antigen). (e.g. col. 9, ll. 50-51). Therefore, the '967 patent provides the motivation to construct a vector comprising a gene encoding a fluorescence marker, an amplifiable selectable marker and a target protein. In addition, **Chishima et al.** teach an expression construct where a GFP gene (S65T) is mobilized into a dicistronic expression vector comprising an amplifiable gene (i.e. DHFR) and a gene expressing a desired product. (Chishima, at 2042, col. 2, ¶3, referring to the pED-mtx resistant construct described in, Kaufman et al. Nucleic Acids Research. 1991, 19(16):4485-90) (Note: this second reference is only being cited to provide information with regard to intrinsic properties of the pED-mtx resistant expression construct not as additional art, See MPEP § 2131.01). Kaufman et al. teach that the pED-mtx resistant construct contains a gene encoding a desired product operably linked to a promoter (i.e. B-lactamase gene, Kaufman, at 4487, Fig. 1). Chishima et al. further teach that the construct replicates in CHO cells. (Chishima, at 2042, col. 2, ¶4).

The above references do not specifically teach wherein the first promoter and the second promoter are mammalian promoters. Crowley teaches the DNA construct is dicistronic, i.e. the selectable gene and product gene are both under the transcriptional control of a single transcriptional regulatory region under the control of promoters such as heterologous mammalian promoters, e.g. the actin promoter (known in the art as a mammalian promoter) or an immunoglobulin promoter, from heat-shock promoters, and from the promoter normally associated with the product gene, provided such promoters are compatible with the host cell systems ((column 13, lines 23-35; column 13, lines 54-64).

Zolotukhin et al, teaches GFF dicistronic expression vector (example VIII, column 49) and discloses expression vectors may comprise one or more constitutive promoters, such as promoters from mammalian genes that are generally active in promoting transcription (column

5, lines 8-17). Zolotukhin teaches examples of constitutive mammalian promoters include various housekeeping gene promoters, as exemplified by the beta actin promoter (column 5, lines 8-17). Zolotukhin teaches using humanized GFP in the context of mammalian promoters for detecting substances that stimulate transcription from a selected promoter in a mammalian or human cell (column 9, lines 37-40).

Therefore, it would have been well within the knowledge of one of ordinary of skill to construct the expression vector to produce the GFP fusion proteins as contemplated by the '967 patent. The ordinary skilled artisan, seeking to develop a construct for expressing proteins that can be easily be monitored via fluorescence and that can be selected for in mammalian cells via amplifiable markers such as DHFR, would have been motivated to incorporate the teachings of the '967 patent or Chishima et al. to construct a expression construct comprising GFP, a selected sequence and DHFR, operably linked to a promoter. It would have been obvious for the ordinary skilled artisan to so construct an expression vector and transfect mammalian cells to express the desired fusion proteins. Furthermore, given the teachings of the cited references and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered that said artisan would have had a reasonable expectation of success in practicing the claimed invention. It would have been prima facie obvious for a person of ordinary of skill in the art seeking to develop a vector with two transcriptional units for isolating cells and purifying the product of interest to combine the respective teachings of Liu taken with Mosser and Bennett by introducing a second transcriptional unit into the first transcriptional unit of Crowley for a coordinated expression of the amplified DHFR marker and the selectable GFP marker in a mammalian cell with a reasonable expectation of success. A person of skill in the art would have been motivated to introduce a second transcriptional unit as taught by the Liu/Mosser/Bennet to the DHFR transcriptional unit of Crowley as a matter of design of choice

amounting to combining prior art elements according to known methods as taught by Liu to yield predictable results. Additionally, given Liu tech direction of transcription by various promoters and the genes they control it would have been obvious for one of ordinary of skill in the art to combine the DHFR and the GFP transcriptional units in order to culture cells in MTX so as to express the gene encoding the product in a selective medium comprising MTX the amplifying agent for sufficient time to allow amplification to occur, whereupon either the desired product is recovered or cells having multiple copies of the product gene are identified as taught by Crowley and particularly since Liu teaches that the coordinate expression of genes in a vector with two transcriptional units results in improved expression of the exogenous gene products which maybe otherwise poorly expressed in a single cell. Moreover, one of ordinary of skill in the art would have been particularly motivated to combine the two transcriptional units since Bennett teaches that GFP fused to a resistance marker integrated as a single cassette, it is reasonable to assume that insertion at a transcriptionally active site that results in high-level expression of the fluorescent selectable marker would also have high expression of the heterologous gene. In addition, since **Zolotukhin** teaches dicistronic expression vectors may comprise one or more constitutive promoters, such as promoters from mammalian genes that are generally active in promoting transcription useful in vivo, e.g., in gene therapy, and in vitro, in screening assays, in screening for the presence of a particular compound within a composition, useful groups of inducible promoters are those activated by heavy metals, P450 gene promoters, activated by a range of toxic compounds; heat shock protein gene promoters such as the hsp70 promoter, which are stimulated by various stresses to name a few examples (column 36-37).

With respect to limitations directed to isolating cells expressing the GFP comprising sorting for and cloning the brightest 1%-10% of fluorescent cells by FACS analysis, it must be noted that where a prior art product teaches the limitation of sorting cells by GFP fluorescence

using a FACS cell sorter, the percentage of fluorescent cells by FACS analysis is a property that is considered intrinsic to FACS cell sorting for which is not something that the Office can determine. Because the Office does not have the facilities for examining and comparing the applicant's product with the products of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed products and the products of the prior art (e.g. that the products of the prior art do not possess the same material structural and functional characteristics of the claimed product). See in re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977). In this case the difference at issue would be GFP FACS sorting and cloning of GFP fluorescent cells in the prior art and the claimed GFP comprising sorting for and cloning the brightest 1%-10% of fluorescent cells.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Supreme Court reaffirmed principles based on its precedent that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." KSR International Co. v. Teleflex Inc. (KSR), 550 U.S. at, 82 USPQ2d at 1395. Thus, the claimed invention as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

A. Applicants argue that Crowley teaches a monocistronic vector in which the polynucleotide encoding the gene of interest is under the control of the same promoter that regulates an amplifiable selectable marker (i.e., DHFR). Crowley neither teaches nor suggests a dicistronic system or the use of GFP.

These arguments are not persuasive because Crowley teaches a dicistronic vector and the elements of the claim 1 as discussed above. Crowley has not been cited fro the GFP expression since this deficiency is cured by the teachings of **Mosser et al** who teaches the use

of plasmid containing a dicisronic expression cassette encoding GFP and a target gene, in a method of screening and selection of cells expressing inducible genes (p 152-153).

B. Applicants argue Liu does not make up the deficiencies of Crowley as Liu teaches a tricistronic vector having three discreet transcriptional units; each with their own promoter and polyadenylation signals. The three separate units express three different gene products. Liu also fails to teach or suggest use of GFP. Moreover, the teachings of Liu and Crowley are fundamentally different from one another and teach away from each other in that Crowley expresses two gene products in a single transcription unit while Liu teaches separation of the gene products into completely separate transcription units. The hypothetical combination of these references undercuts the strategy of each, and is therefore would not be made by one of ordinary skill in the art.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, in contrast to Applicants assertion Liu teaches dicistronic and tricistronic vectors and Liu is specifically cited for teaching a second transcription unit comprising a second promoter and an intron positioned 3' of the second promoter as required in step (ii) of the instant invention. Liu teaches the tissue-specific plasminogen activator (tPA) gene and expressing the resulting chimeric gene behind the CMV promoter with the CMV intronA (see example I).

C. Applicants argue Mosser also does not help in making up the deficiencies of Crowley, even in view of Liu. Mosser teaches a different strategy entirely. Mosser describes on p. 151 that the strategy was to "eliminate the time-consuming process of screening individual clones by transient transfection." Mosser first transfects target cells with a vector that expresses

the hygromycin-resistance gene linked to a tetracycline-responsive element and selects the cells using hygromycin. This serves to establish a tTA-expressing cell line in which to introduce further vectors (see Mosser, p. 160, first column, lines 23-27). Subsequently, a hygromycin-resistant population is transfected with a second vector which may contain what Mosser describes as a "dicistronic vector" containing a gene of interest and GFP. Notably, Mosser's dicistronic vector uses a single promoter to express both the gene of interest and GFP on a single transcript separated by an IRES sequence (see Mosser, p. 156).

These arguments are not persuasive because Mosser is cited for cure the deficiency for introducing a GFP gene into the dicistronic vector of Crowley which is well known in the art to introduce a GFP gene into the dicistronic vector of Crowley which contains the DHFR selectable marker. Applicants are reminded as discussed in the rejection above Crowley teaches a dicistronic vector that created one transcript and Bennett and Tan provide motivation to combine the expression of DHFR and GFP in a dicistronic vector. This is because Bennett teaches plasmids are integrated as a single cassette, it is reasonable to assume that insertion at a transcriptionally active site that results in high-level expression of the fluorescent selectable marker would also have high expression of the heterologous gene (p 482, 1st column) and Tan teaches a dicistronic vector comprising both a fluorescence encoding gene (i.e. GFP) and an amplifiable selectable marker (i.e. DHFR) can be used. (e.g. col. 9, ll. 40-45) (emphasis added).

D. Applicants argue Chishima teaches a GFP gene mobilized on a vector expressing DHFR and a desired protein (i.e., 13-1actamase). However, beta-lactamase is a protein that is produced by bacteria and confers resistance to beta-actam antibiotics (e.g., penicillin). Incorporation of beta-lactamase in the pED vector is to allow propagation of the vector in bacterial cells. Thus, the promoter used in producing beta-lactamase is a prokaryotic promoter, not a eukaryotic promoter as instantly claimed. Moreover, the prokaryotic promoter

would not be functional in mammalian cells and thus, beta-lactamase would not be expressed at all. Thus, Chishima does not teach a vector system to express a protein of interest with GFP and an amplifiable selectable marker and does nothing to make up for the fundamental deficiencies of the above references.

These arguments are not persuasive because as discussed in the rejection Chishima et al. teach an expression construct where a GFP gene (S65T) is mobilized into a dicistronic expression vector comprising an amplifiable gene (i.e. DHFR) and a gene expressing a desired product. (Chishima, at 2042, col. 2, ¶3, referring to the pED-mtx resistant construct described in, Kaufman et al. Nucleic Acids Research. 1991, 19(16):4485-90) (Note: this second reference is only being cited to provide information with regard to intrinsic properties of the pED-mtx resistant expression construct not as additional art, See MPEP § 2131.01). Kaufman et al. teach that the pED-mtx resistant construct contains a gene encoding a desired product operably linked to a promoter (i.e. B-lactamase gene, Kaufman, at 4487, Fig. 1). Chishima et al. further teach that the construct replicates in CHO cells. (Chishima, at 2042, col. 2, ¶4).

Conclusion

No Claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571)272-3305.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paras Peter can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Magdalene K. Sgagias, Ph.D.
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/Anne-Marie Falk/
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